Epigenetics & cancer

Present by : Sanaz Zebardast

Under supervision : Dr . Gheibi

31 December 2016

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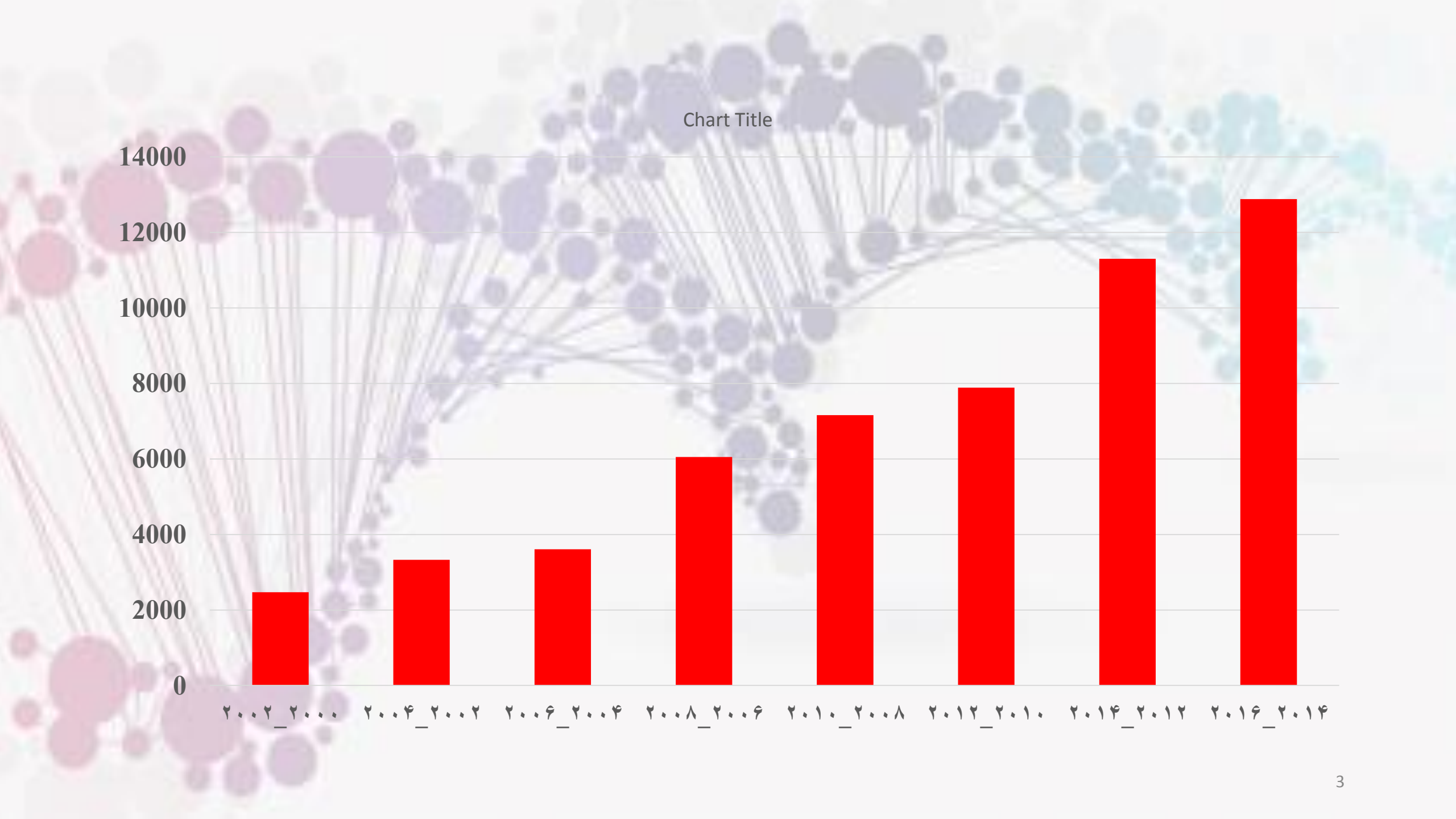
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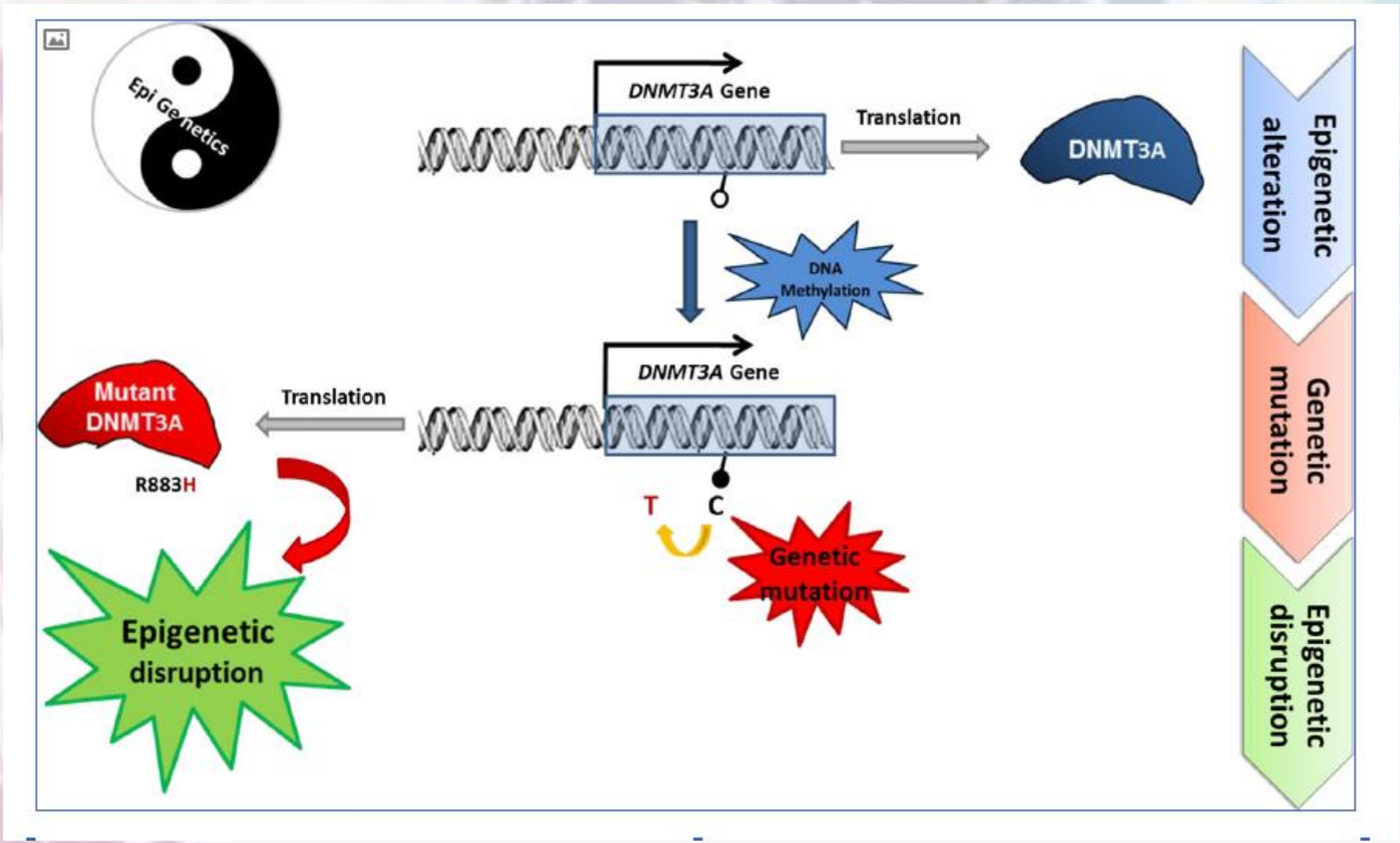
Introduction (1)

- Heritable alterations that are not due to changes in DNA sequence
- Alter DNA accessibility and chromatin structure
- Regulate patterns of gene expression
- Crucial for normal development and differentiation
- Crucial for regulation of pluripotency genes


Epi Genetics
DNMT3A Gene
Translation
DNMT3A
DNA Methylation
DNMT3A Gene
Translation
Mutant DNMT3A
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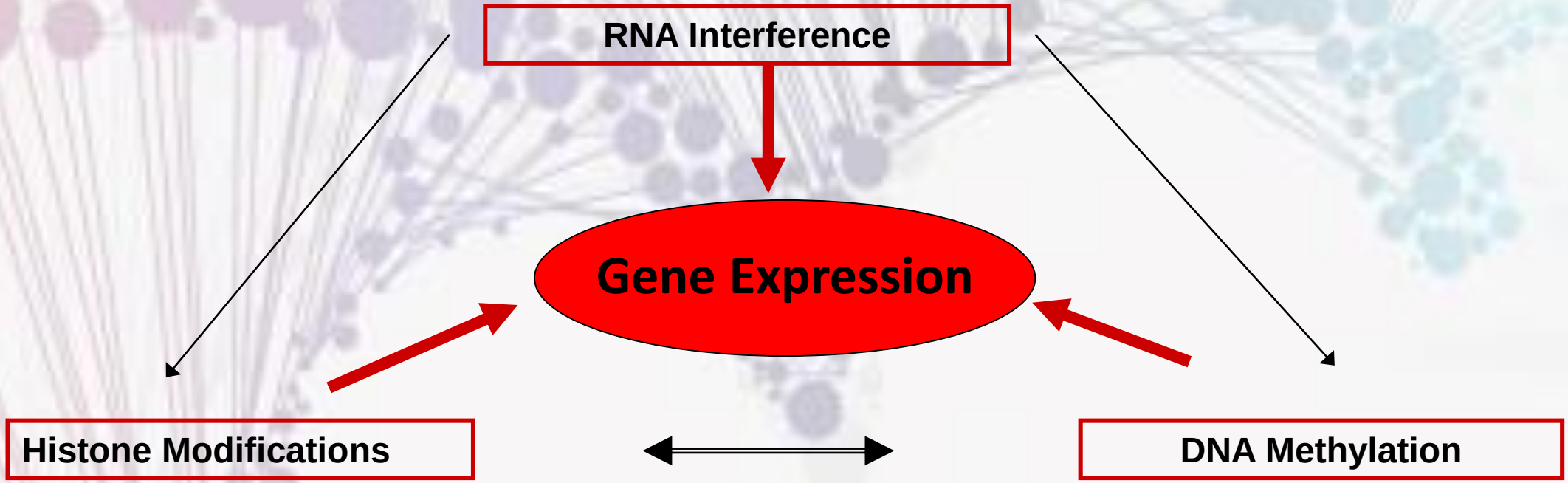
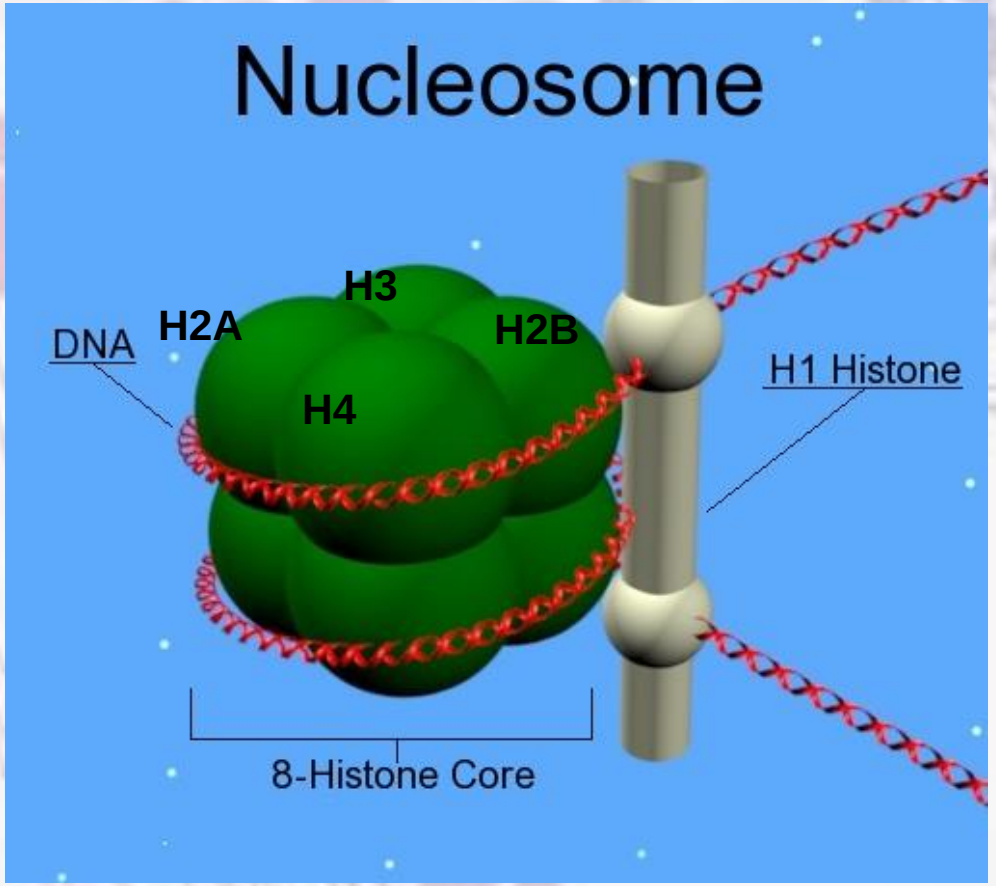
Genetic mutation
Epigenetic disruption
Epigenetic alteration
Genetic mutation
Epigenetic disruption

(2)

Epigenetic mechanisms



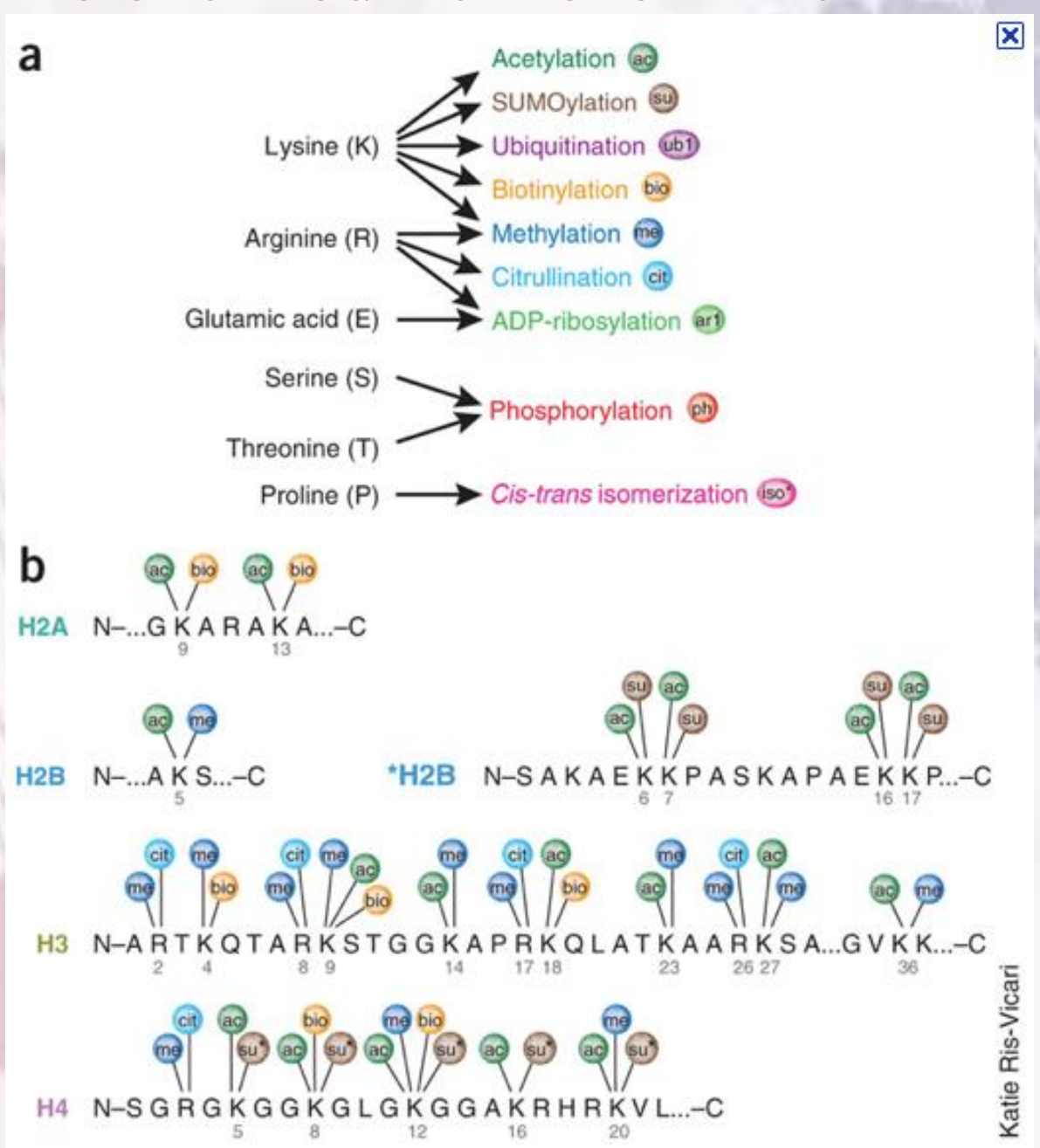
Nucleosome

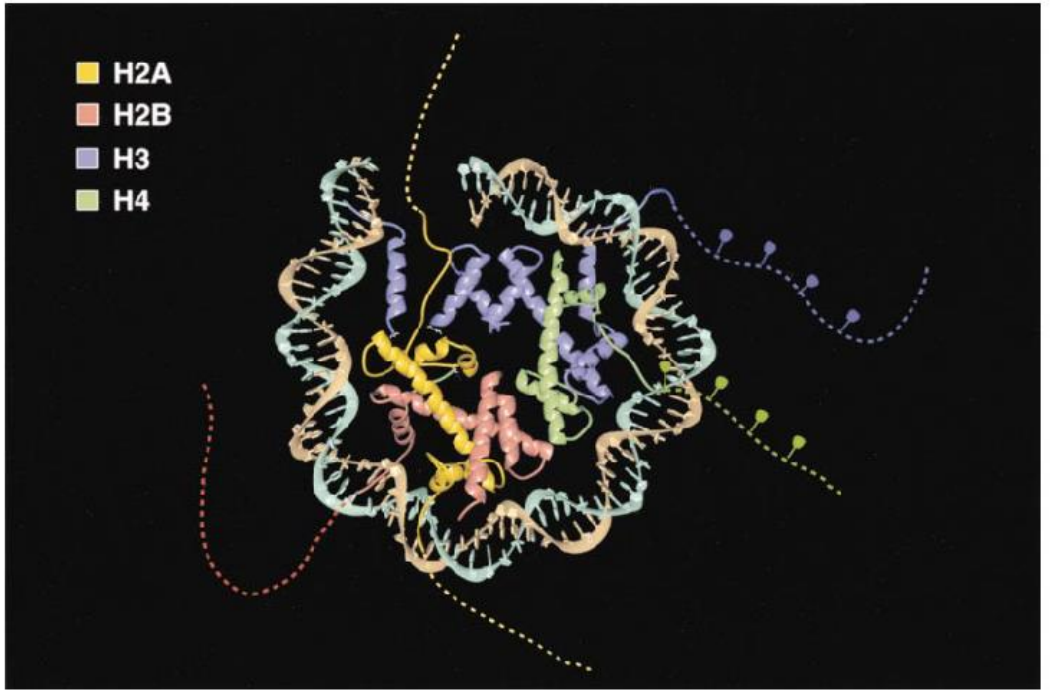


- **The basic repeating unit of chromatin.**
- **It is made up by five histone proteins: H2A, H2B, H3, H4 as core histones and H1 as a linker.**
- **It provides the lowest level of compaction of double-strand DNA into the cell nucleus.**
- **It often associates with transcription.**

1974: Roger Kornberg discovers nucleosome who won Nobel Prize in 2006.

Histone modifications matter





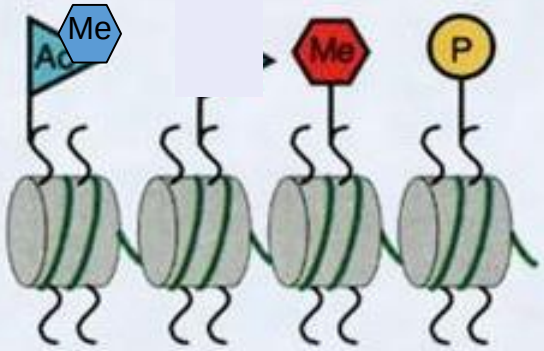
Histone tails are modified, this influences accessibility of the genomic DNA

Latham and Dent
Nat Struct Mol Biol 2007

Structure & Epigenetics of Euchromatin versus Heterochromatin

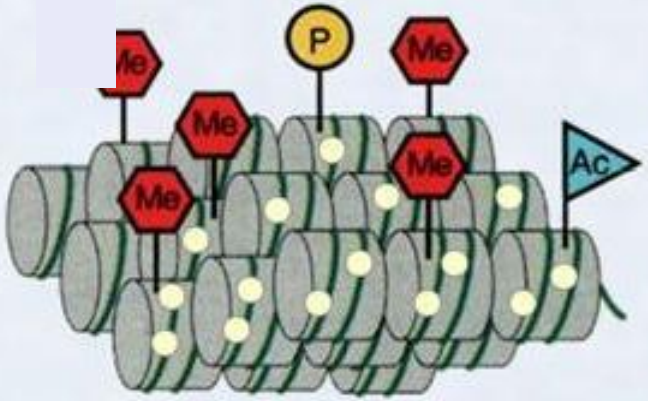
DNA methylation and histone modifications help to compartmentalize the genome into domains of different transcriptional potentials

Euchromatin



- High histone acetylation
- Low DNA methylation
- H3-K4 methylation

Heterochromatin



- Low histone acetylation
- Dense DNA methylation
- H3-K9 methylation

Paula Vertino, Henry Stewart Talks

Histon modifying enzymes

Acetyltransferase	Substrates
HAT1	H4 (K5, K12)
GCN5, PCAF	H3 (K9, K14, K18)
CBP, P300	H3 (K14, K18), H4 (K5, K8), H2AK5, H2B (K12, K15)
TIP60/PLIP	H4 (K5, K8, K12, K16), H3K14
HBO1	H4 (K5, K8, K12)
Lysine methyltransferases	**Substrates**
SUV39H1–2	H3K9
G9a	H3K9
EuHMTase/GLP	H3K9
ESET/SETDB1	H3K9
CLL8	H3K9
MLL1–5	H3K4
SET1A-B	H3K4
ASH1	H3K4
SET2	H3K36
NSD1	H3K36
SYMD2	H3K36
DOT1	H3K79
Pr-SET7/8	H4K20
SUV4 20H1–2	H4K20

Deacetylases	Substrates
SirT2–3	H4K16
Lysine demethylases	**Substrates**
LSD1/BHC110	H3 (K4, K9)
JHDM1a-b	H3K36
JHDM2a-b	H3K9
JMJD2A/JHDM3A, JMJD2B-C	H3 (K9, K36)
JMJD2D	H3K9
JARID1A-D	H3K4
UTX	H3K27
JMJD3	H3K27
Serine/threonine kinases	**Substrates**
Haspin	H3T3
MSK1–2	H3S28
CKII	H4S1
Mst1	H2BS14
Rsk2	H3S10
Ubquitilases	**Substrates**
Bmi/Ring1a	H2AK119
RNF20/RNF40	H2BK120
Arginine methyltransferases	**Substrates**
CARM1	H3 (R2, R17, R26)
PRMT4	H4R3

(3)

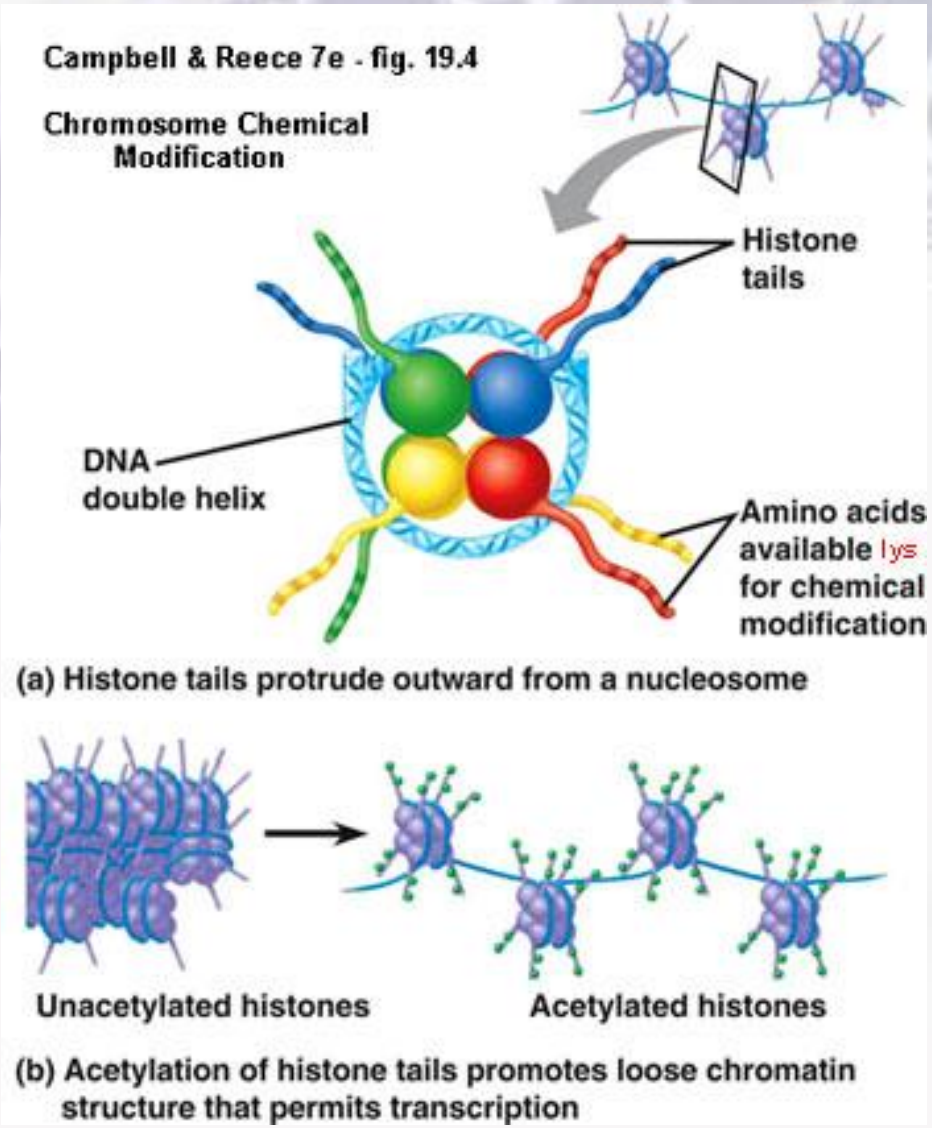
Effector proteins

Histone modification	Binding modules	* Effector proteins (Target histone)
Methylation	Chromodomain	HP1 (H3K9), PC (H3K27), CHD1 (H3K4)
	Tudor	JMJD2A (H3K4)
	MBT	L3MBTL1 (H1bK26, H4K20)
	PHD	BPTF (H3K4), ING2 (H3K4)
	SRA	UHRF1 (H3K9)
Acetylation	Bromodomain	Rsc4 (H3K14), Bdf1 (H4K8), Taf1 (H4K16)
Phosphorylation	14-3-3	14-3-3 protein (H3S10)

* A few representative effector proteins containing the specified binding module are shown with the target histone modification recognized by them in parentheses.

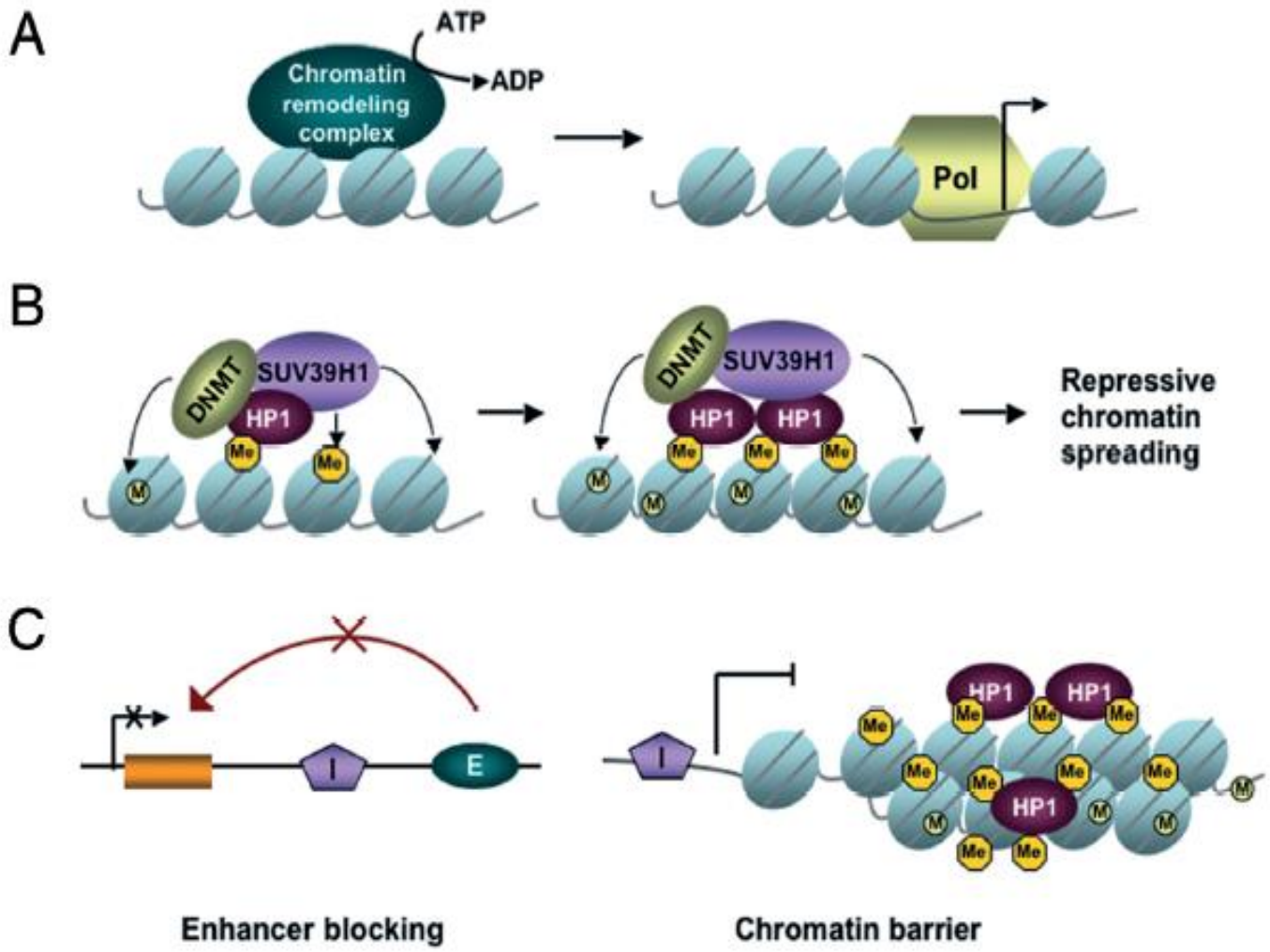
(3)

Histone acetylation



http://porpax.bio.miami.edu/~cmallery/150/gene/c7.19.4.histone.mod.jpg

Other nuclear proteins crucial for epigenetic modifications



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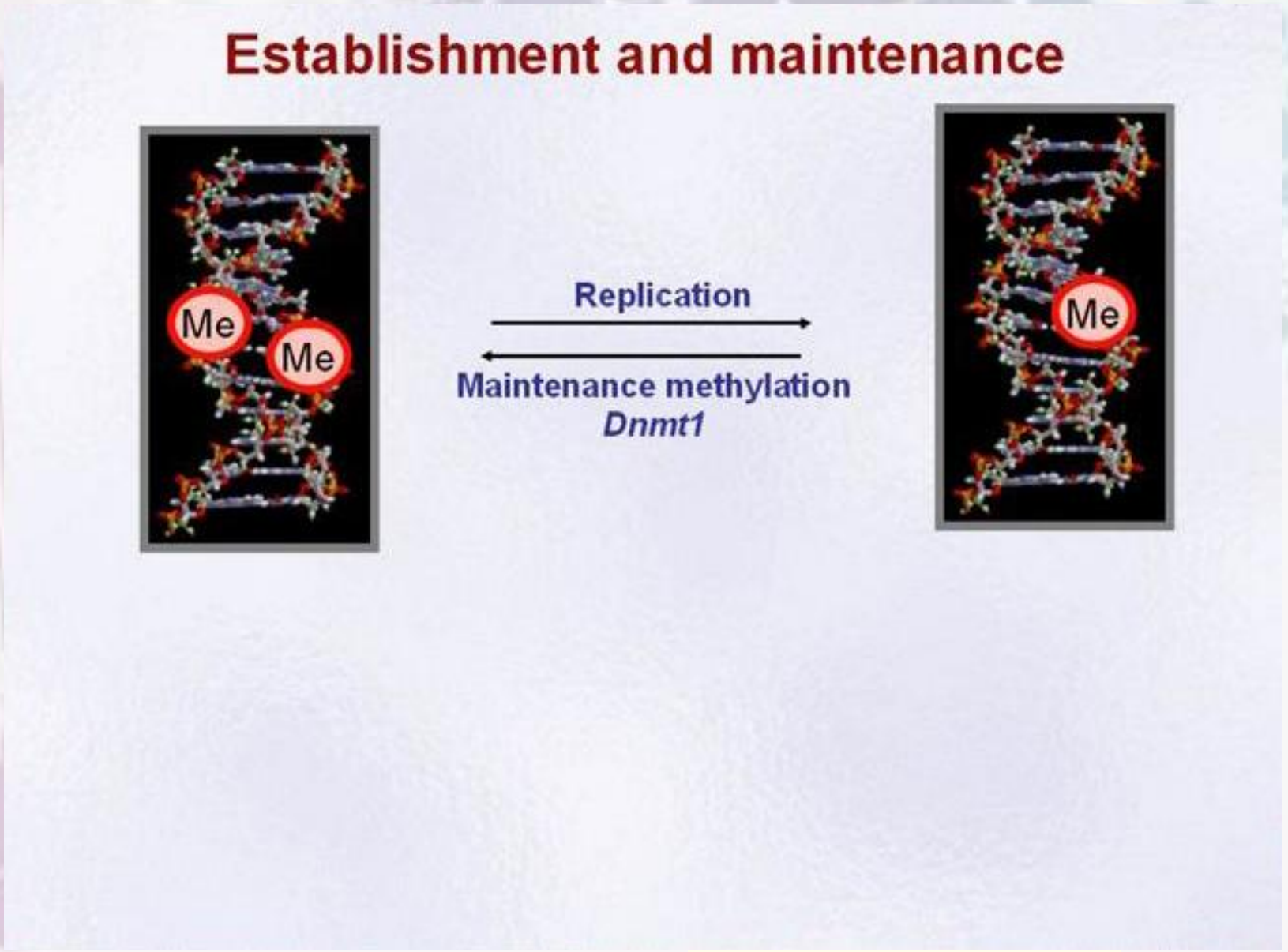
DNA methylation & Epigenetic (3)

- In mammalian genome methylation occurs in C5
- Methylation patterns are stable and inheritable
- Reproramming occurs in 2 developmental stages
- DNMT3A and DNMTB are denovo methyltransferases
- DNMT1s are maintenance methyltransferases

Other DNMTS (3)

- Unlike DNMT1 & DNMT3A/B , DNMT2 has only catalytic domain
- DNMTL expresses only in germ cell for de novo methylation
- DNMTL modulates the catalytic activity of DNMT3A & DNM3TB

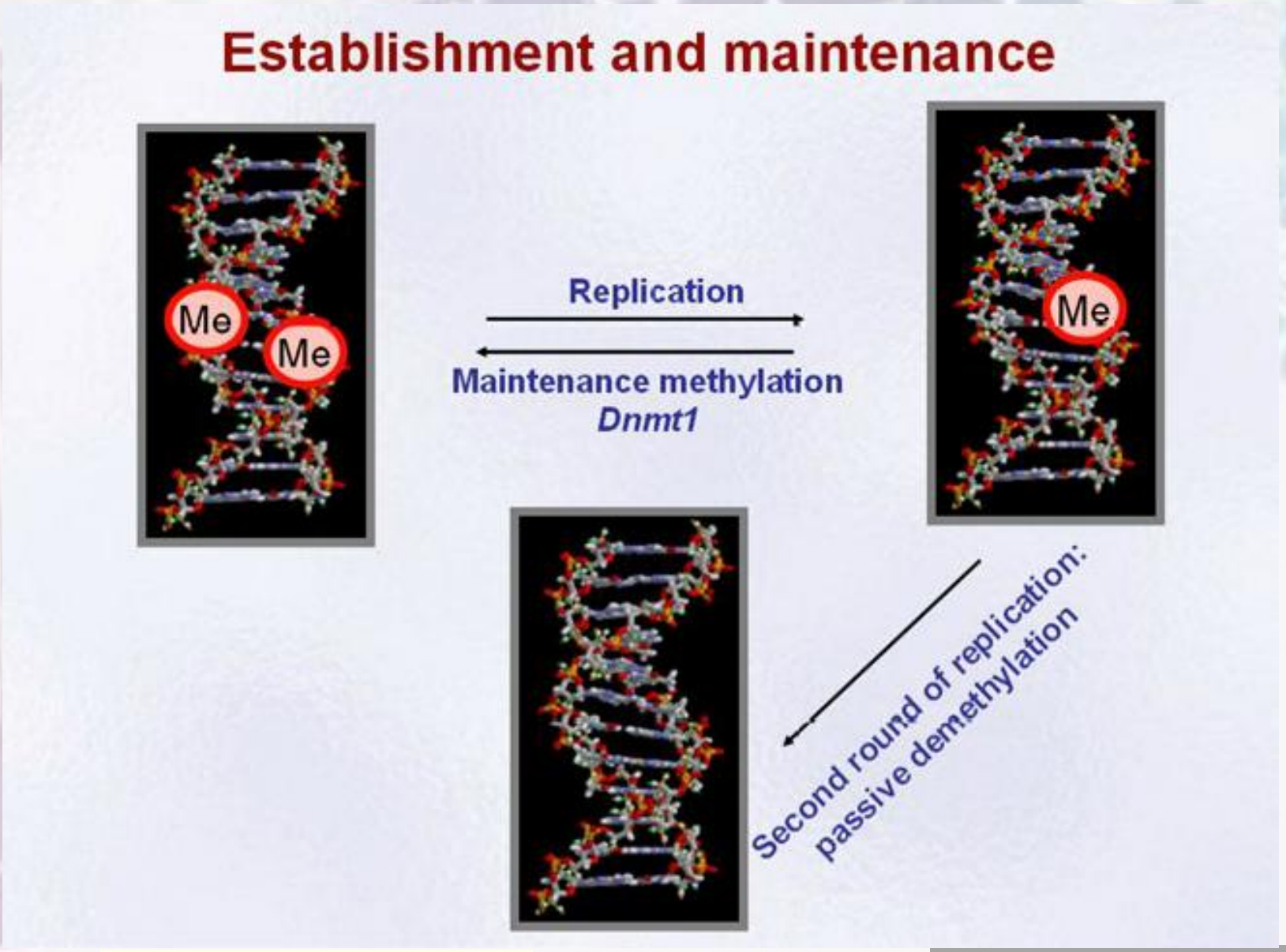
Maintenance of Cytosine Methylation



Alex Meissner, Henry Stewart Talks

Alex Meissner, Henry Stewart Talks

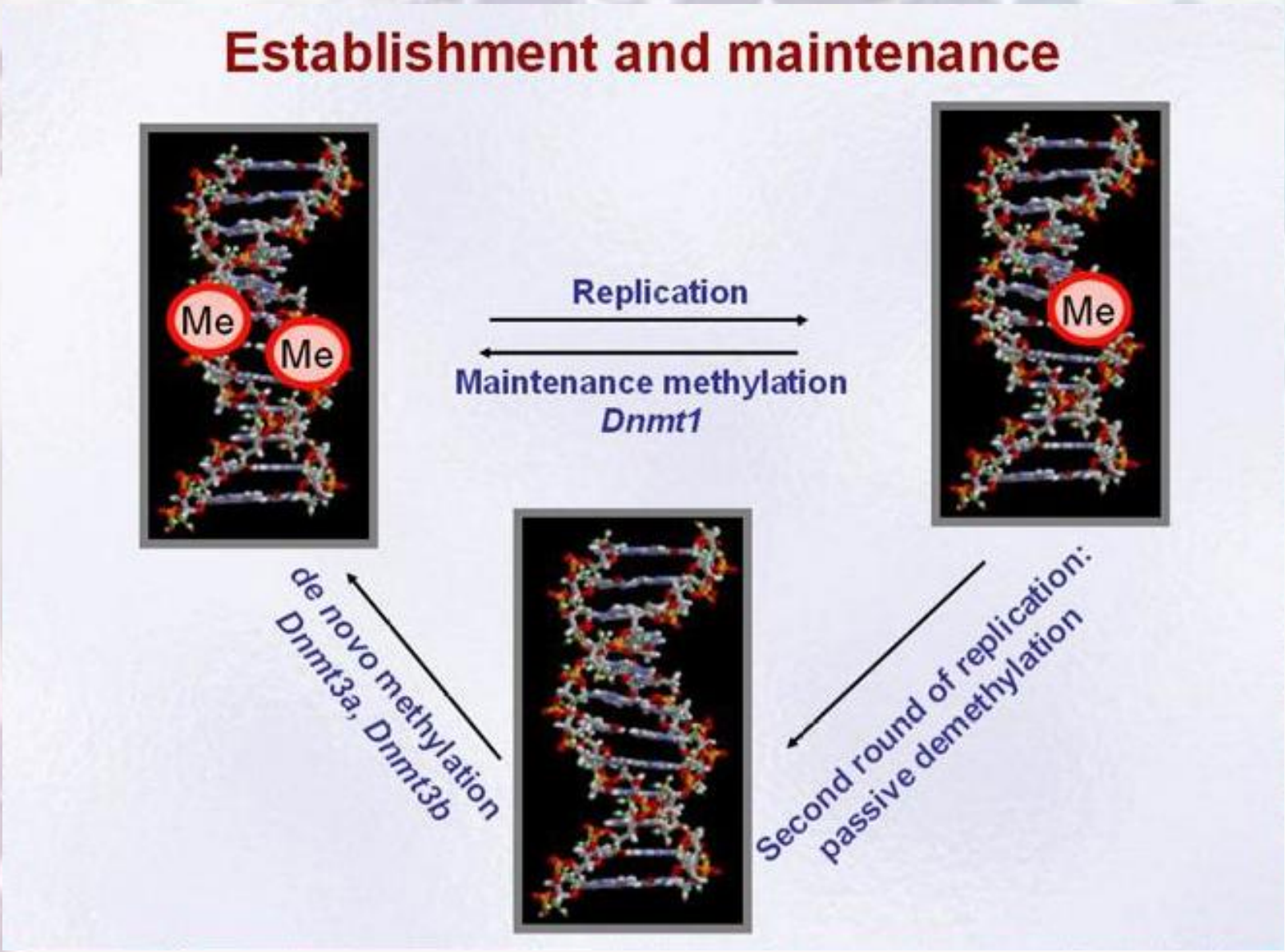
Passive Demethylation of 5-Methyl-Cytosine



Alex Meissner, Henry Stewart Talks

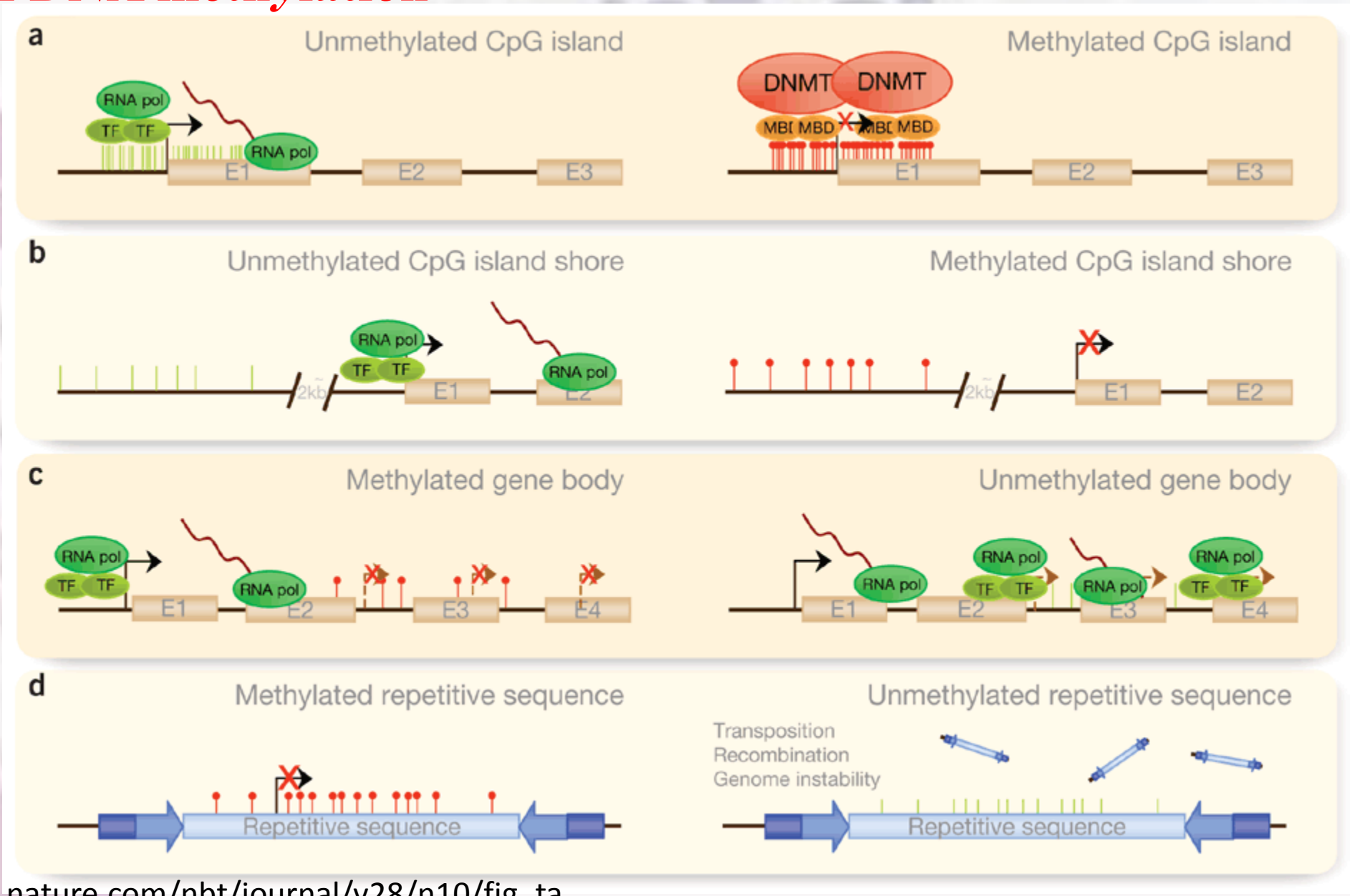
Alex Meissner, Henry Stewart Talks

Establishment and Maintenance of Cytosine Methylation



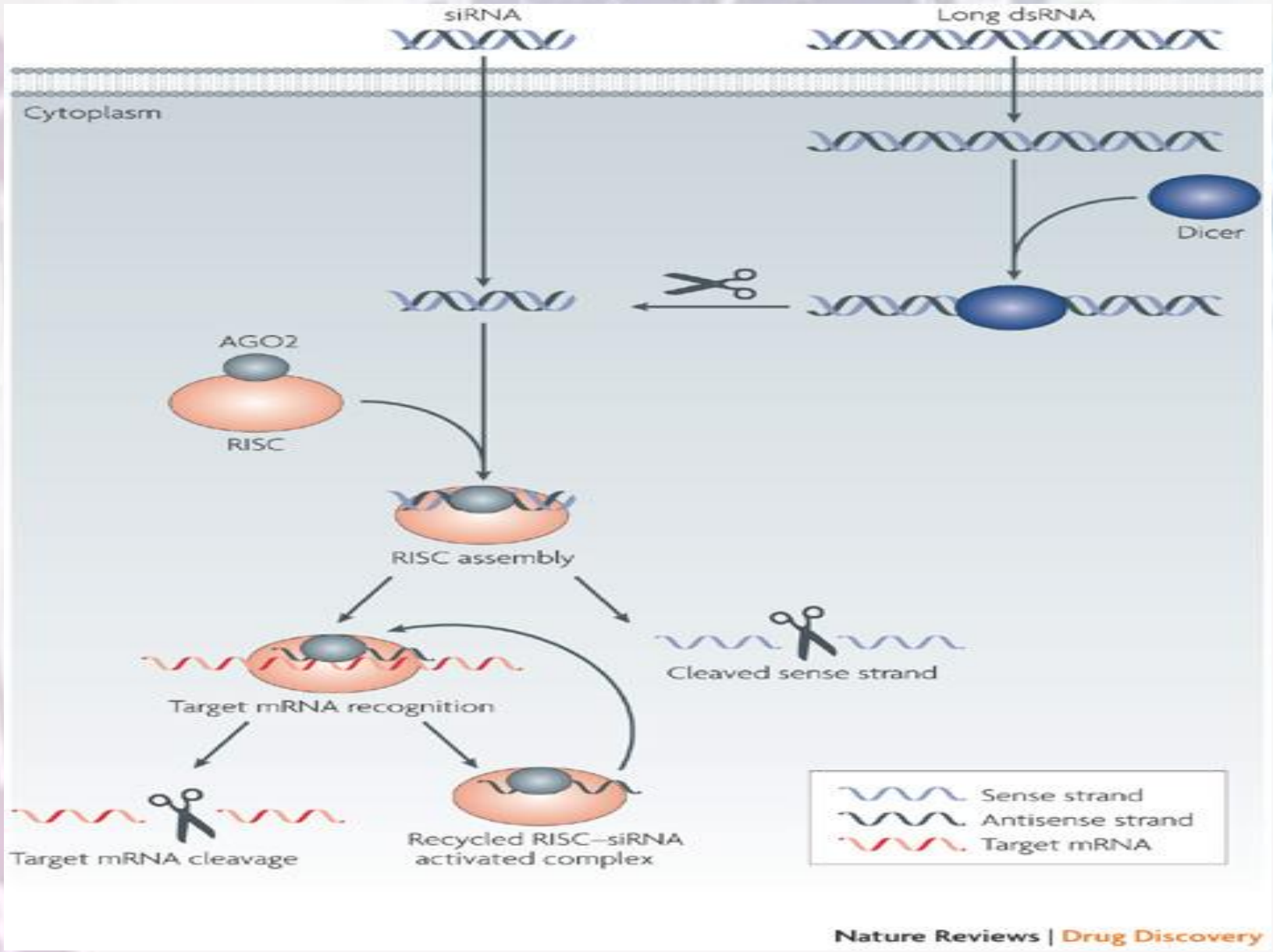
Alex Meissner, Henry Stewart Talks

Regions of DNA methylation



http://www.nature.com/nbt/journal/v28/n10/fig_tab/nbt.1685_F1.html

RNA Interference (RNAi)



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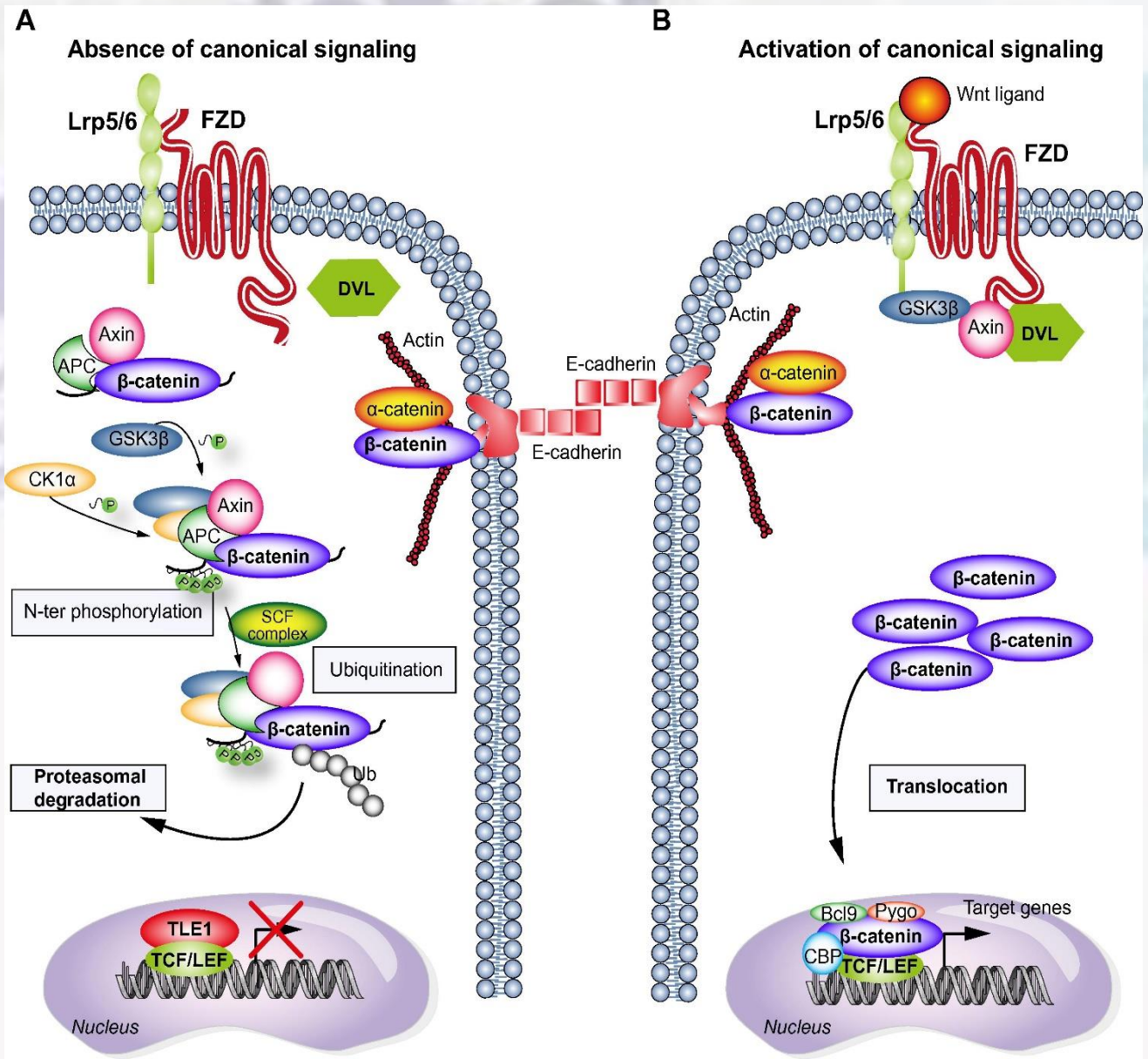
http://www.nature.com/ncpneuro/journal/v3/n7/images/ncpneuro0551-f1.jpg

Wnt signaling pathway (5)

- Conserved pathway that has crucial regulation role
- Cell fate determination , cell migration , cell polarity , neural patterning and organogenesis during embryonic development
- Require for adult tissue maintenance
- Perturbations in it promote both human degenerative diseases and cancer
- Theraputic reagents are aimed for controlling wnt signaling

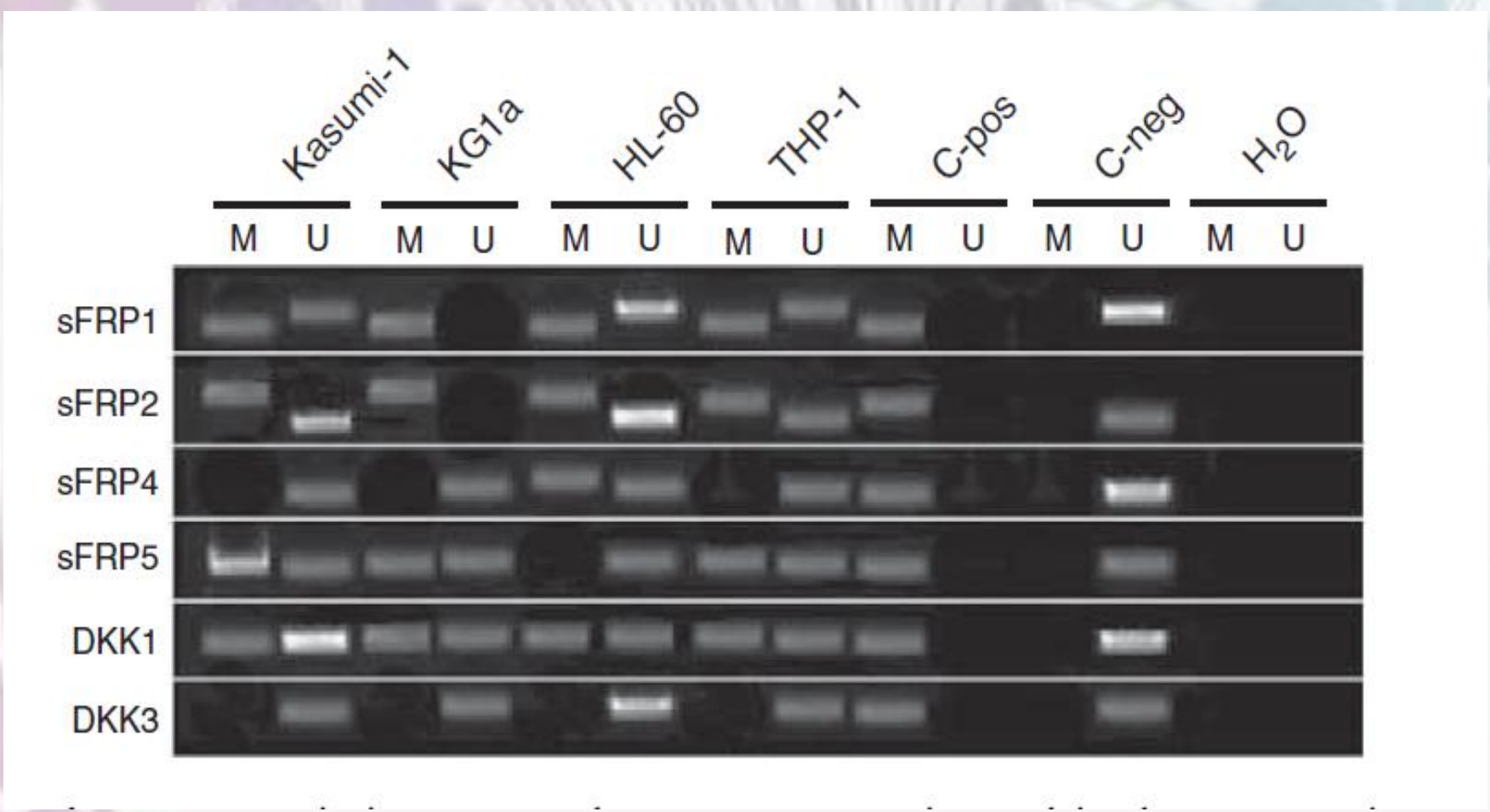
Wnt signaling pathway



Wnt signaling pathway & Epigenetic (6)

- Activation of wnt signaling pathway in the leukemia
- The promoter methylation status of wnt antagonists (sFRP 2,4,5 & DKK1,3) has been analyzed
- Aberrant methylation of them was detected by MSP (methylation-specific polymerase chain reaction)
- Function of epigenetic regulation of wnt pathway in predicting relapse in a subgroup of AML

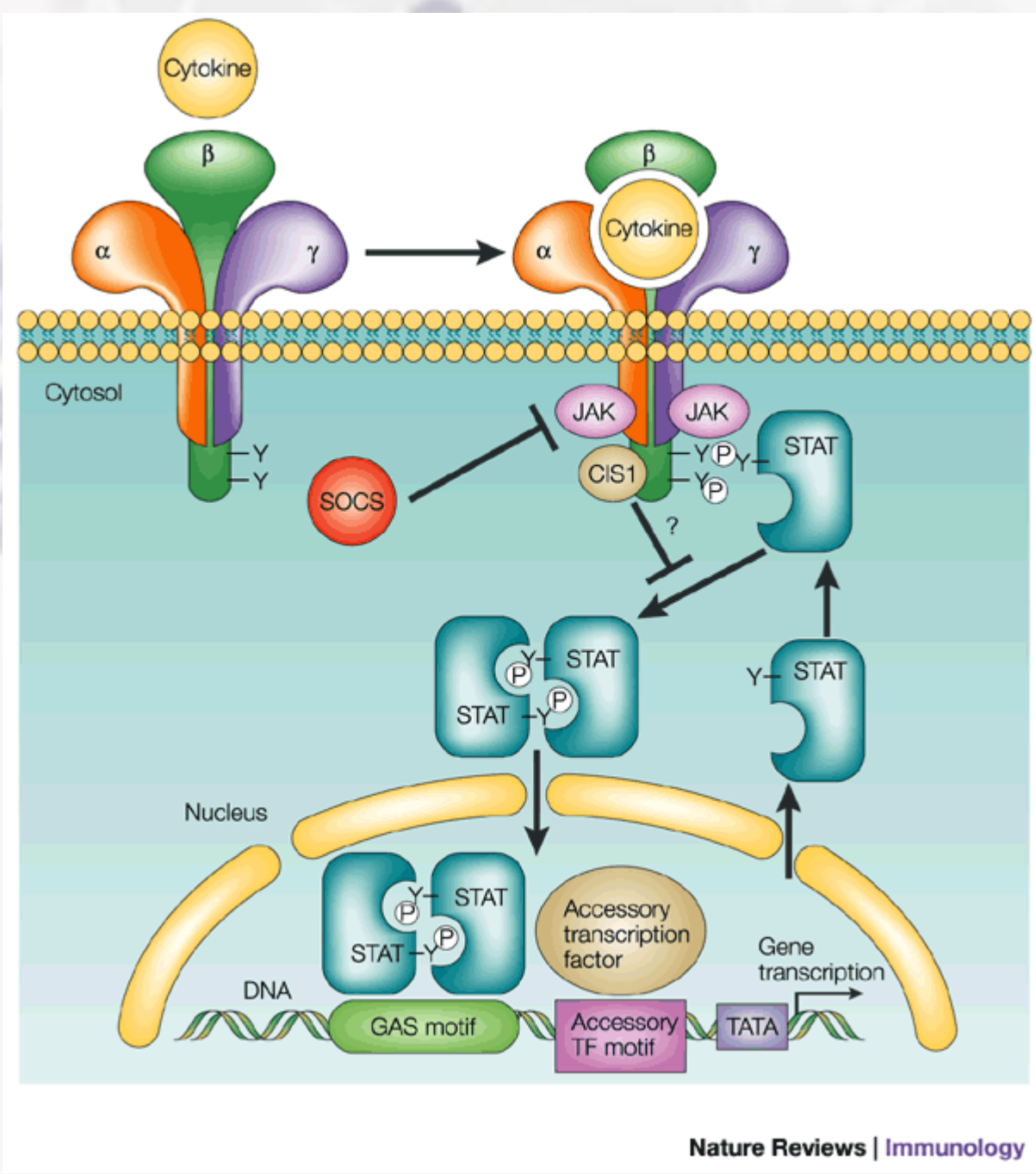
Msp analysis in AML (acute myeloid leukemia) cell lines (6)



Jak-stat signaling pathway (7)

- Regulates embryonic development
- In the control of processes such as stem cell maintenance , haematopoiesis & inflammatory response
- Aberrant activation confers malignant properties on cancer cells
- A productive strategy for drug development

JAK/STAT Pathway

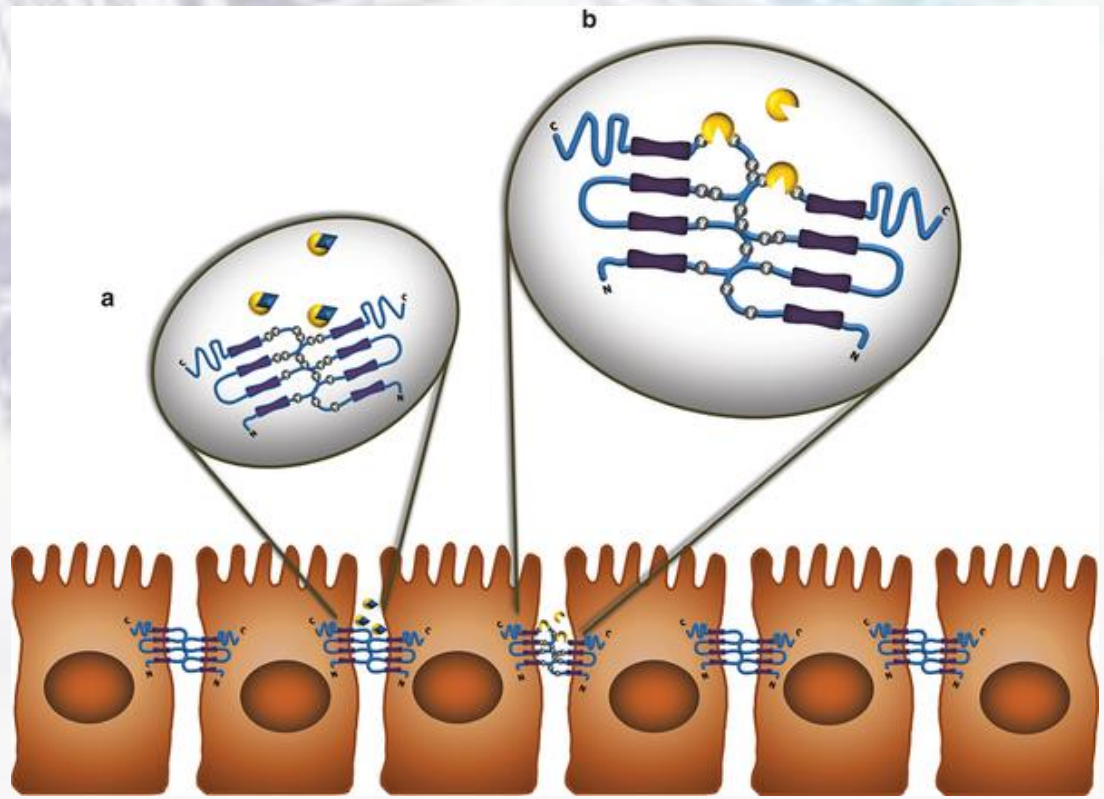


Jak/STAT signaling pathway & epigenetic (8)

- SOCS1 and SHP1 negatively regulate Jak/STAT signaling pathway
- promoter hypermethylation is investigated in myeloma
- SHP1 : primarily express in hematopoietic cells & is tumor suppressor gene
- Socs1 : cytokine-inducible negative regulators of the cytokine signaling

Epigenetic role on integral proteins (9)

- Occludin is the first identified integral protein for tight junction (tj)
- Its long COOH-terminal domain receive and transmit cell survival signal
- Loss of tj –associated molecules correlate with tumor progression
- Occludin expression is silenced by CpG island hypermethylation
- Forced expression of occludin in cancer cells leads to acting apoptogenic factors

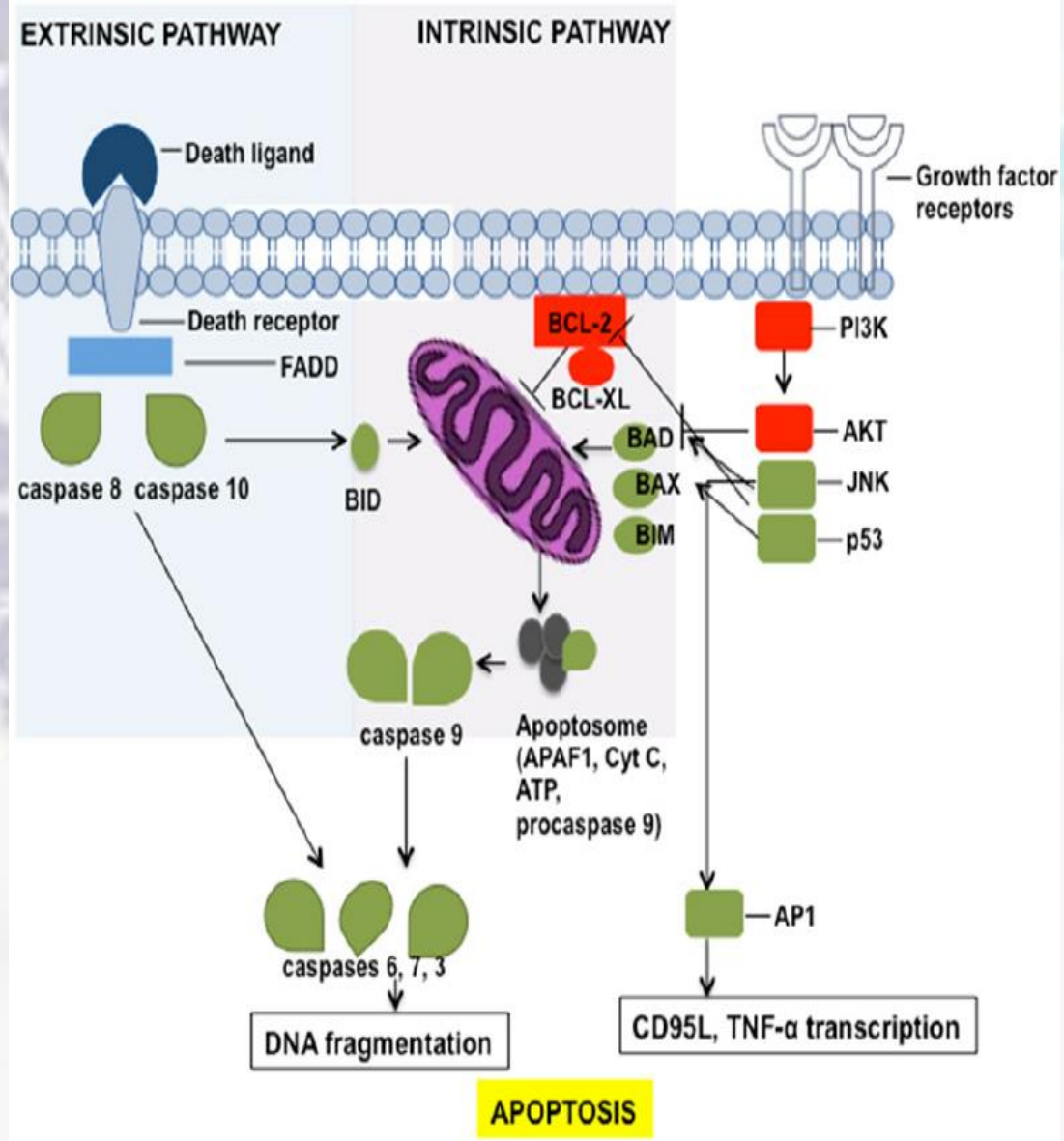


Epigenetic & apoptosis (10)

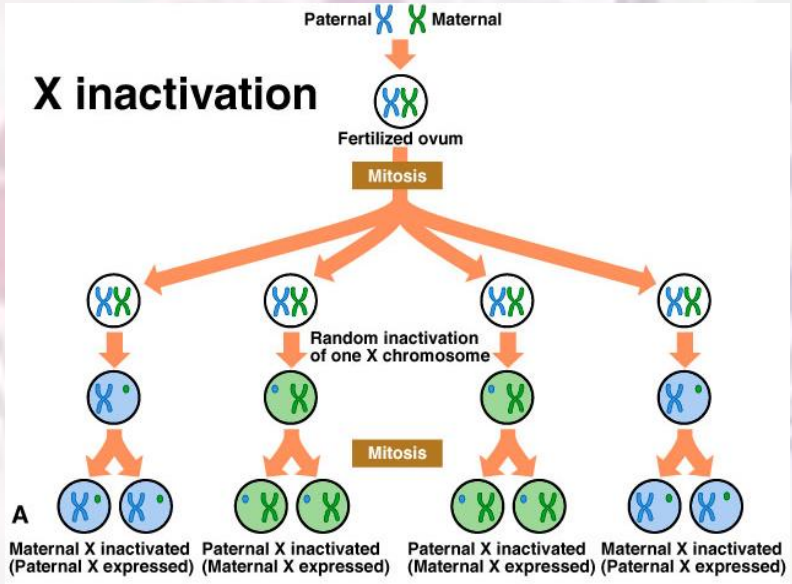
- Some hematopoietic disease (CLL) fails apopotosis B-cell
- Nuclear factor kB (NFkB) mediated expression of antiapoptotic molecules
- Glycogen synthase kinase-3B (GSK3B) regulates (NFkB)
- They accumulate in the nucleus of CLL B cells

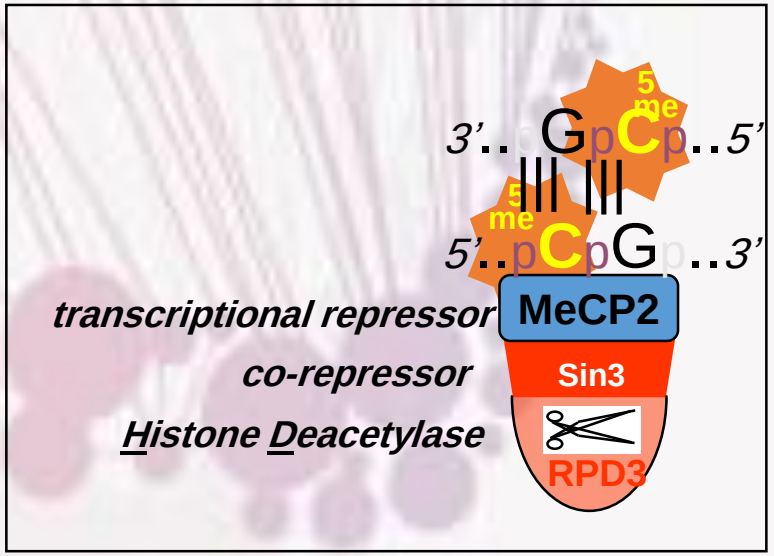
Epigenetic & apoptosis

- Pharmacologic inhibition of GSK-3 leads to decrease expression of Bcl-2 & XIAP
- Abrogating binding is through an epigenetic mechanism
- GSK-3 is a potential therapeutic target in the treatment of CLL



Epigenetic & X-chromosome Inactivation

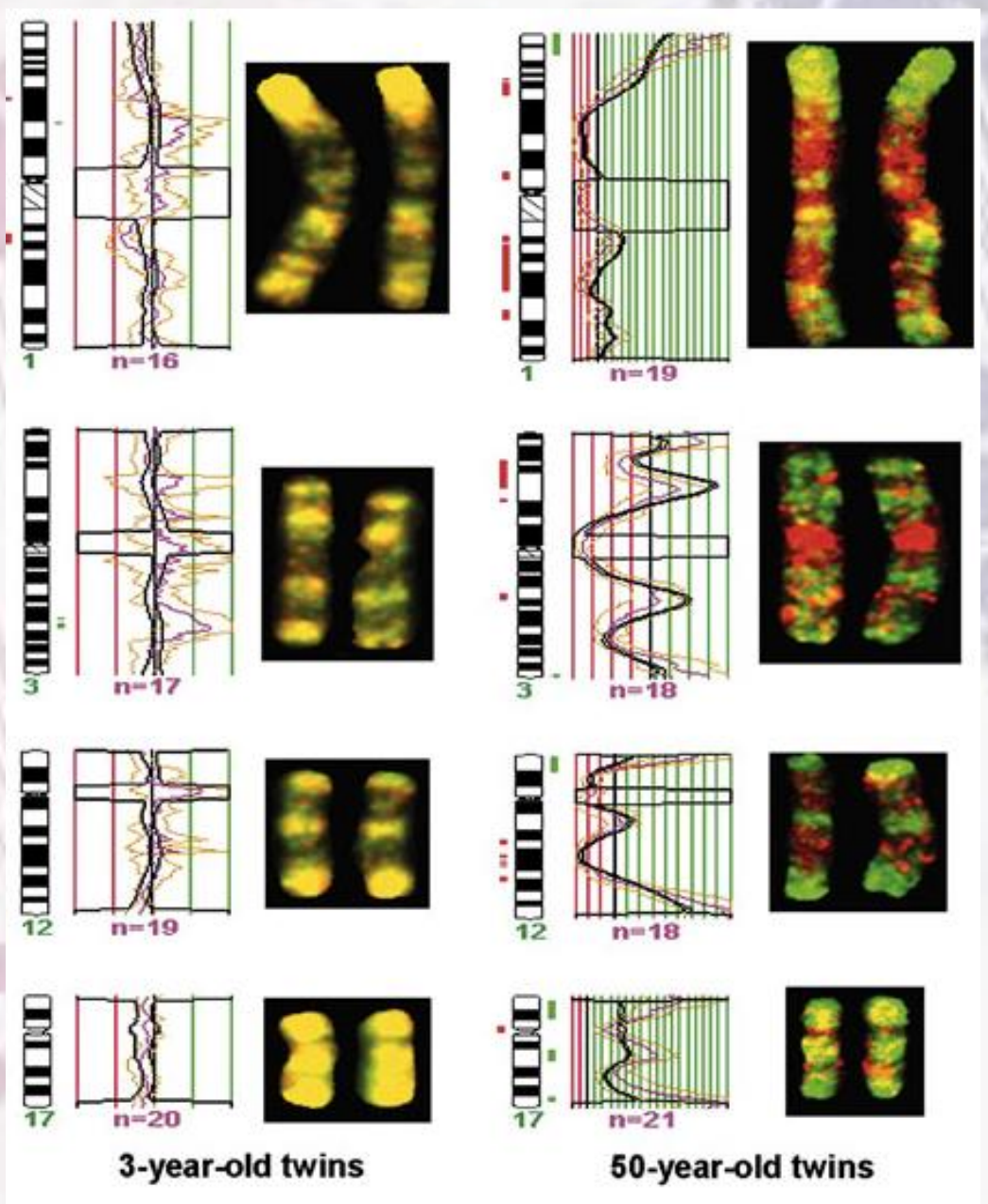




- In X-inactivation (lyonization) one of the two copies of the X chromosome present in female mammals is inactivated.
- The inactive X chromosome is silenced by packaging in repressive heterochromatin.
- The choice of which X chromosome will be inactivated is random .
- Silencing initiated at Xic/XIC and spreads along chromososme.
- 5meC CpG DNA modification is observed in inactivated X chromosomes.
- 5meC binds transcriptional repressor MeCP2 (MethylC-binding Protein-2).
- MeCP2 binds Sin3 with RPD3 histone deacetylase.

Source: Jones et al. Nat.Genet. 19, 187 (1998)

Differences in the epigenome of monozygotic twins



The difference in the twins' epigenomes is what makes them become different when they are older

The epigenetic tags can have such an effect on the twins that one can develop a disease while the other is fine

When this situation occurs, researchers will try to pinpoint the environmental factors that are responsible for the disease

Fraga et al. PNAS, 2005

conclusion

- that differing amounts in methylation can play a role in an animal's behavior
- Failures in epigenetic are likely to play a role in the majority of cancer
- Since most of the studies on epigenetics have been conducted on rodents, it will be interesting to see if their conclusions carry over into humans


Thank You

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